Stability analysis of multi compartment models for cell production systems

JOINT WORK WITH PHILIPP GETTO, ANNA MARCINIAK-CZOCHRA, MARIA DEL MAR VIVANCO AND TOMAS ALARCON

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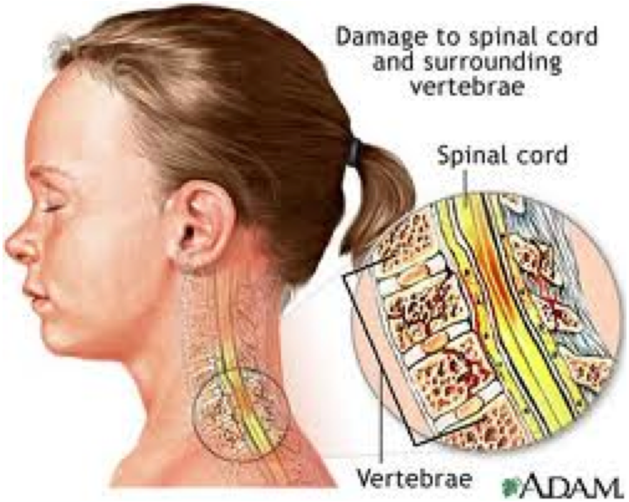
- Basic mechanisms for stem cell development
- Modeling and analysis
  - ODE modeling
  - DDE modeling (Future work)
- Discussion

Why Stem cells?

Beike Biotechnology (China) develops therapies for disorders based on adult stem cells.

Optic nerve hypoplasia

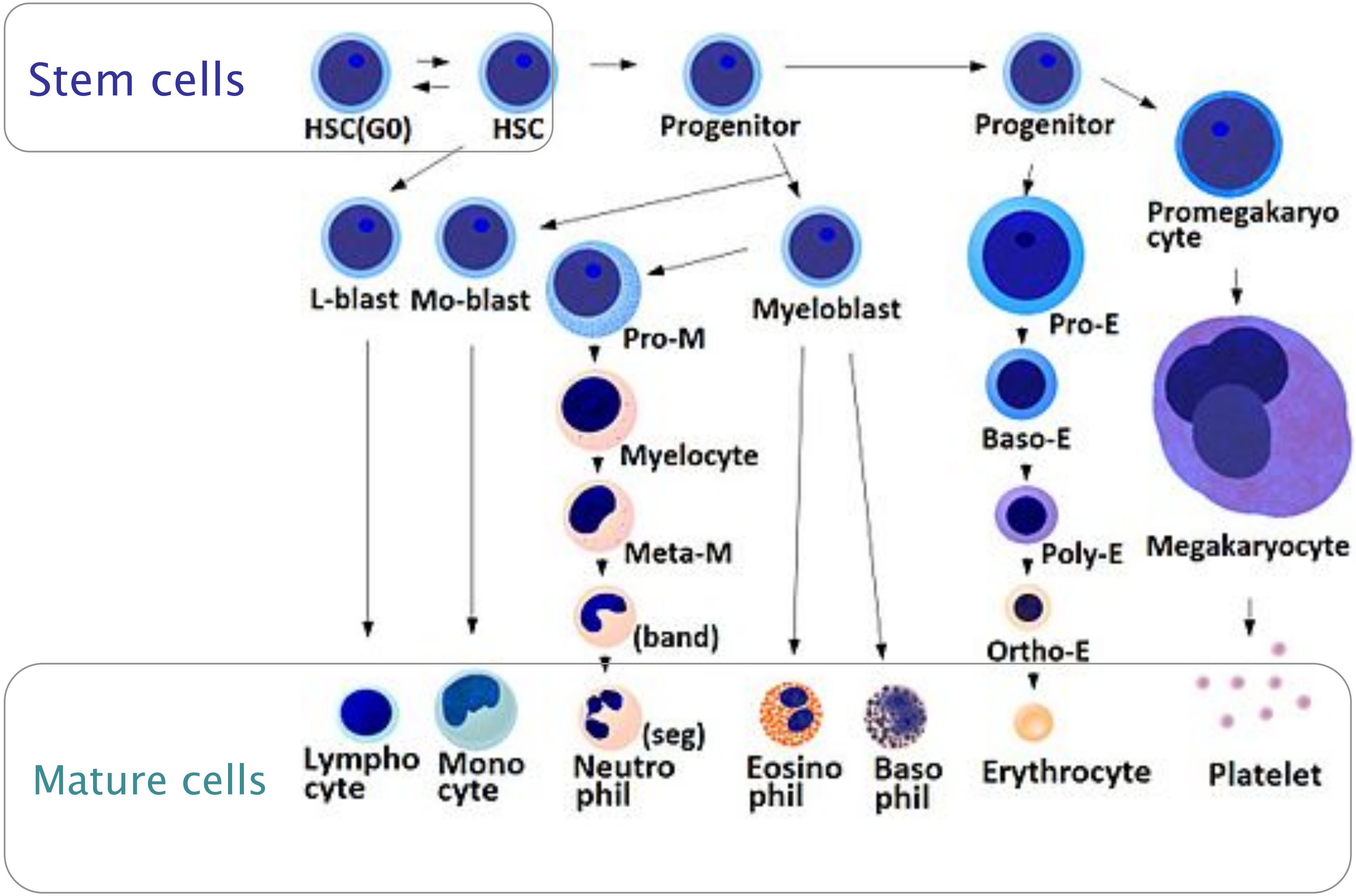


Spinal cord injury

- ✓ have been injected into about 9,300 patients
- ✓ USD 26,000 for the procedure
- ✓ BUT stem cell treatments are NOT READY for those clinical use.

potential to dramatically change the treatment of human disease

Example: Hematopoietic stem cells



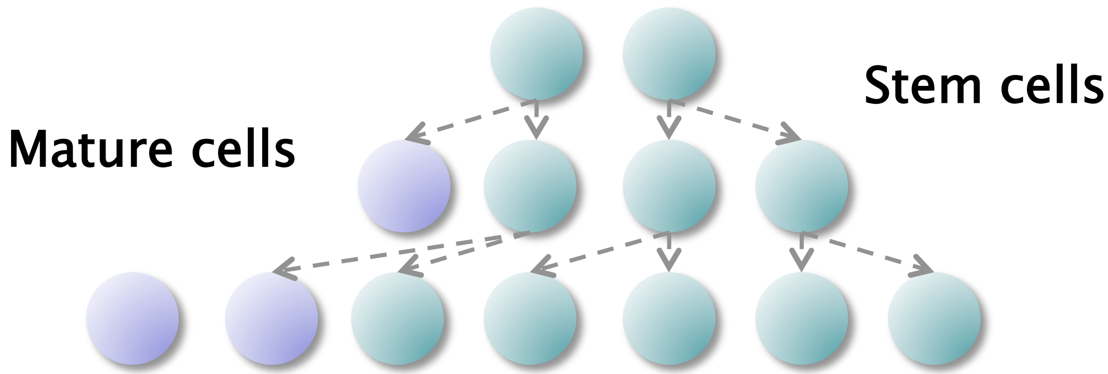
Hematopoietic stem cell, Wikipedia

Differentiation and self-renewal

2 stem cells

2x2 daughter cells

3x2 daughter cells



Fraction of self-renewal $s(t) \in [0,1)$

Division rate $d(t)$

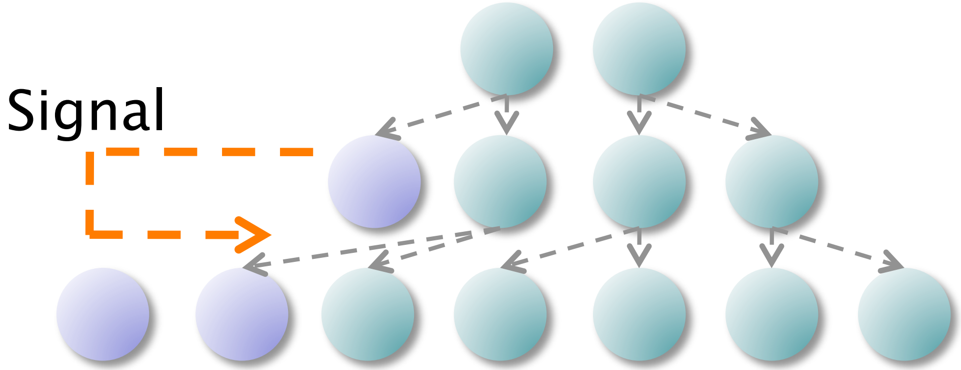
	Inflow/unit time	Outflow/unit time
Stem cells, w(t)	$2s(t)d(t)w(t)$	$d(t)w(t) + \mu_w w(t)$
Mature cells, v(t)	$2(1-s(t))d(t)w(t)$	$\mu_v v(t)$

Stem cells / Mature cells

$$\begin{cases} w'(t) &= (2s(t)-1)d(t)w(t) - \mu_w w(t), \\ v'(t) &= 2(1-s(t))d(t)w(t) - \mu_v v(t), \end{cases}$$

Extracellular signal feedback

Signal (cytokine etc) intensity depends on the amount of mature cells



Regulated fraction of self-renewal $s(t) := s_w(v(t)) := \dfrac{a_w}{1+kv(t)}$

Regulated division rate $d(t) := d_w(v(t)) := \dfrac{p_w}{1+kv(t)}$

$$\begin{cases} w'(t) &= (2s(t)-1)d(t)w(t) - \mu_w w(t), \\ v'(t) &= 2(1-s(t))d(t)w(t) - \mu_v v(t), \end{cases}$$

Stem cells
Mature cells

$$\begin{cases} w'(t) &= (2s_w(v(t))-1)d_w(v(t))w(t) - \mu_w w(t), \\ v'(t) &= 2(1-s_w(v(t)))d_w(v(t))w(t) - \mu_v v(t), \end{cases}$$

Marciniak-Czochra et al., (2008), Nakata et al., (appear)

Problems and strategy

Biological problem	Modeling and analysis	Interpretation

Stability of the stem cell pool

How can they maintain homeostasis?– regulation mechanism	Stability of equilibria	Investigate Influence of the model parameters on the stability

Maturation process

How do they mature? –The number of maturation stages.	Models with and without intermediated stage	Examine outcomes from two models

2-compartment models and their stability analysis

Scenario 1: Regulation of the division rate

$$\begin{cases} w'(t) &= (2a_w - 1)d_w(v(t))w(t) - \mu_w w(t), \\ v'(t) &= 2(1-a_w)d_w(v(t))w(t) - \mu_v v(t). \end{cases}$$

$$d_w(v) = \frac{p_w}{1+kv}$$

Reproduction number

$$R_w = \frac{(2a_w - 1)\,p_w}{\mu_w}.$$

	Trivial eq. (0,0)	Positive eq. (w,v)
$R_w < 1$	GAS=Globally Asymptotically Stable	
$R_w > 1$	Exists	GAS

Scenario 2: Regulation of the fraction of self-renewal

$$\begin{cases} w'(t) &= (2s_w(v(t)) - 1)p_w w(t) - \mu_w w(t), \\ v'(t) &= 2(1-s_w(v(t)))p_w w(t) - \mu_v v(t), \end{cases}$$

$$s_w(v) = \frac{a_w}{1+kv}$$

Reproduction number

$$S_w := \frac{2a_w p_w}{p_w + \mu_w}.$$

	Trivial eq. (0,0)	Positive eq. (w,v)
$S_w < 1$	GAS	
$S_w > 1$	Exists	GAS

PROOF by Lyapunov functions

Lyapunov function for positive eq.

Scenario 1

$$L_1(t,w(t),v(t)) := \frac{1}{\mu_w}L_{11}(t,w(t),v(t)) + \frac{1}{\mu_v}L_{12}(t,w(t),v(t)).$$

$$L_{11}(t,w(t),v(t)) := \frac{w(t)}{w_1} - 1 - \ln\frac{w(t)}{w_1},$$

$$L_{12}(t,w(t),v(t)) := \frac{v(t)}{v_1} - 1 - \frac{1}{v_1}\int_{v_1}^{v(t)} \frac{d_w(\xi)}{d_w(v_1)}d\xi.$$

Scenario 2

$$L_2(t,w(t),v(t)) := \frac{1}{p_w G(v_2)}L_{21}(t,w(t),v(t)) + \frac{1}{\mu_v}L_{22}(t,w(t),v(t)).$$

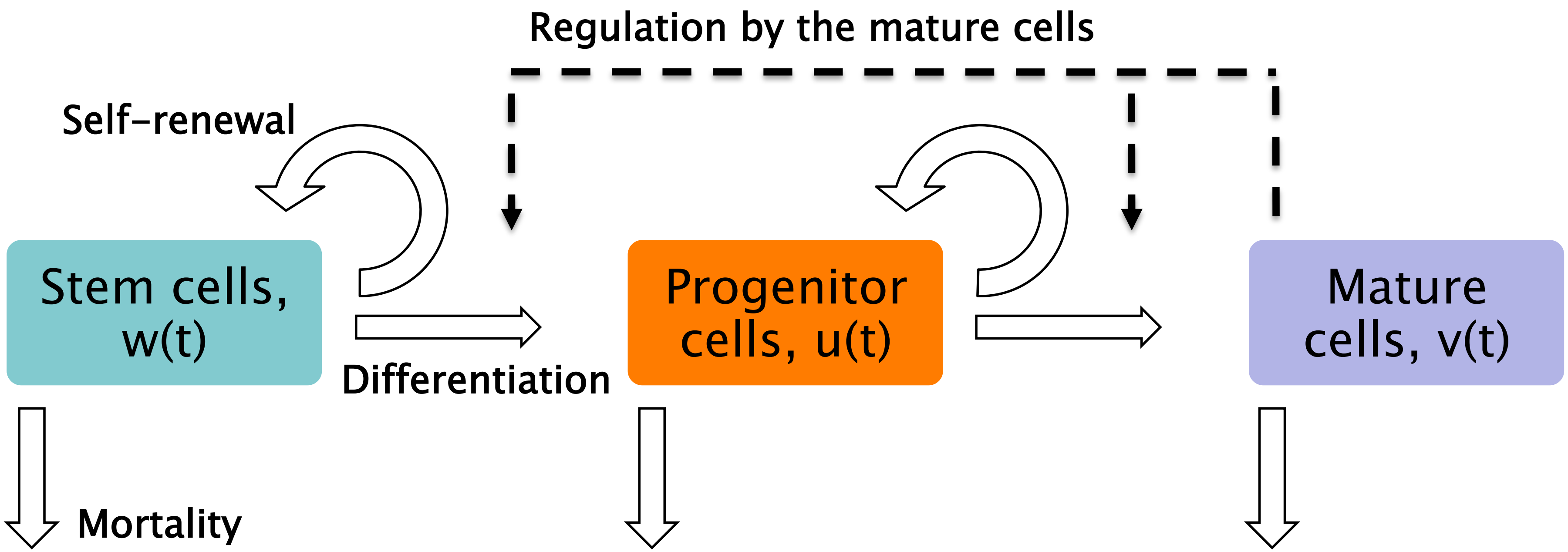
$$G(v) := 2\left(1 - s_w(v)\right) \text{ for } v \geq 0.$$

$$L_{21}(t,w(t),v(t)) := \frac{w(t)}{w_2} - 1 - \ln\frac{w(t)}{w_2},$$

$$L_{22}(t,w(t),v(t)) := \frac{v(t)}{v_2} - 1 - \frac{1}{v_2}\int_{v_2}^{v(t)} \frac{G(v_2)}{G(\xi)}d\xi.$$

3-compartment model

Nakata Y., Getto Ph., Marciniak-Czochra A., Alarcon T., *J. Biological Dynamics* (in press)



Progenitor cells, u(t)

$$\begin{cases} w'(t) &= (2a_w - 1)\,\frac{r_w}{1+kv(t)} w(t) - w(t), \\ u'(t) &= (2a_u - 1)\,\frac{r_u}{1+kv(t)} u(t) + 2\,(1 - a_w)\,\frac{r_w}{1+kv} w(t) - m_u u(t), \\ v'(t) &= 2\,(1 - a_u)\,\frac{r_u}{1+kv(t)} u(t) - m_v v(t), \end{cases}$$

Existence and stability of equilibria

Reproduction number of stem cells: $R_w := (2a_w - 1)r_w$

Reproduction number of progenitor cells $R_u := \dfrac{(2a_u - 1)r_u}{m_u}$

Existence and stability of equilibria

	Trivial eq. (0,0,0)	No SC eq. (0,u,v)	**Positive eq. (w,u,v)**
$R_w < 1$, $R_u < 1$	LAS		
$R_u > 1$, $R_u > R_w$	Exists	LAS	
$R_w > 1$, $R_w > R_u$	Exists	Exists	Exists

How about the stability of the positive equilibrium?

Stability region in three parameters plane

Let $\alpha := (2a_u - 1) r_u$
Stability boundary in (α, m_v, m_u) plane

Theorem:
Let us assume that $R_w > 1$ holds.
1) For $(\alpha, m_v) \in \Omega \setminus (A_1 \cup A_2)$ the positive equilibrium is LAS if

$$m_u > \max\{0, \rho(\alpha)\}$$

holds.

2) For $(\alpha, m_v) \in A_1$ the positive equilibrium is LAS if

$$m_u > \xi_+(\alpha, m_v)$$

and is unstable if

$$0 < m_u < \xi_+(\alpha, m_v).$$

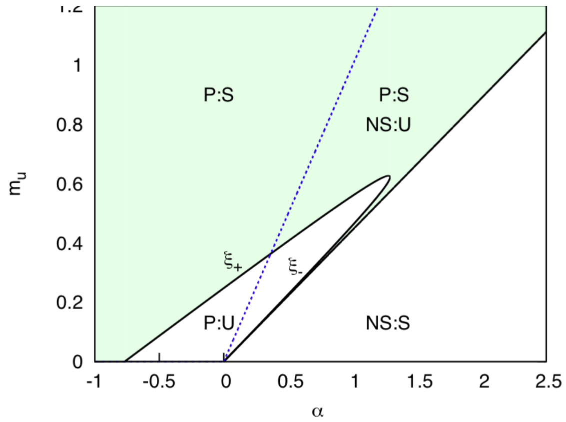
3) For $(\alpha, m_v) \in A_2$ the positive equilibrium is LAS if

$$m_u > \xi_+(\alpha, m_v) \text{ or } \xi_-(\alpha, m_v) > m_u > \rho(\alpha)$$

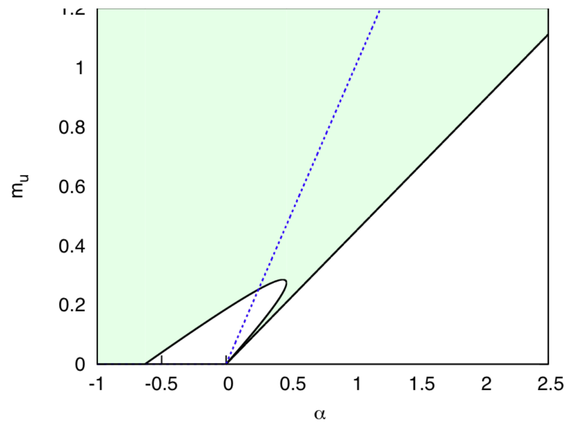
and is unstable if

$$\xi_-(\alpha, m_v) < m_u < \xi_+(\alpha, m_v).$$

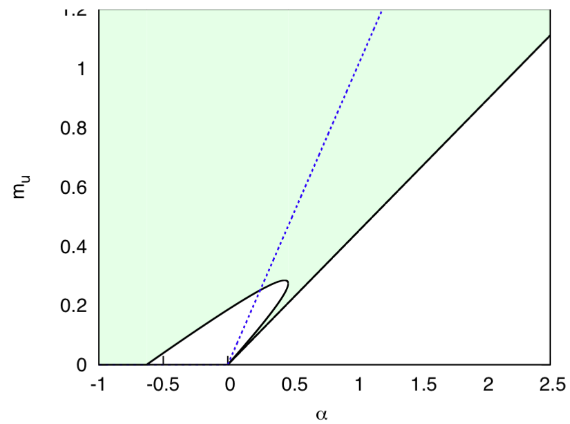
Stability region of the positive and no stem cell eq.



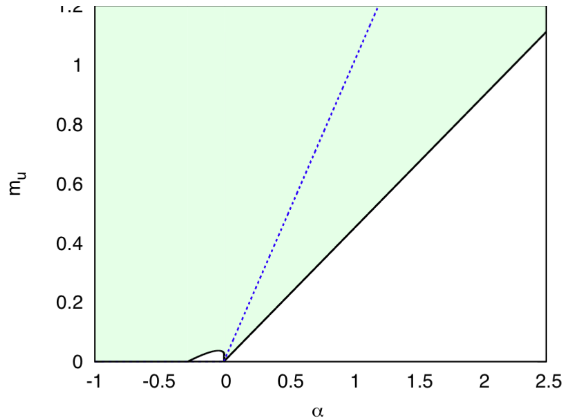
$m_v = 0.01$



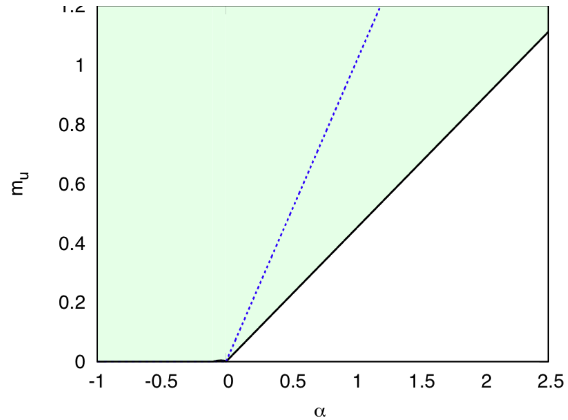
$m_v = 0.05$



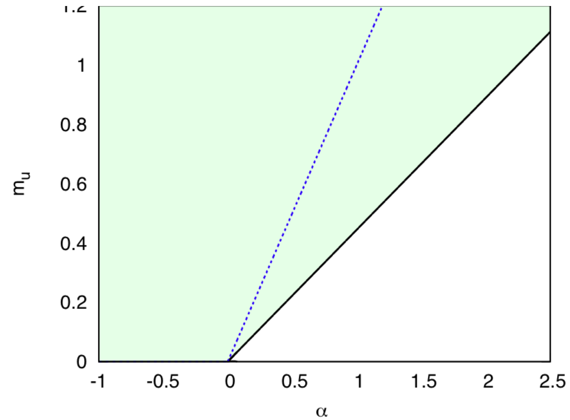
$m_v = 0.10$



$m_v = 0.15$



$m_v = 0.20$



$m_v = 0.25$

The instability region shrinks as mv increases

PROOF

1. Characteristic equation about the positive equilibrium

$$0=\lambda\left[\left\{\lambda+m_u\left(1-\frac{R_u}{R_w}\right)\right\}\left\{\lambda+m_v\left(2-\frac{1}{R_w}\right)\right\}+m_v m_u\left(1-\frac{1}{R_w}\right)\right]+m_u m_v\left(1-\frac{R_u}{R_w}\right)\left(1-\frac{1}{R_w}\right).$$

2. Applying Routh-Hurwitz condition

$$F_{(x,y)}(m_u)=m_u^2+\varphi_1(x,y)\,m_u+\varphi_2(x,y)\,,\ \text{for}\ (x,y)\in\Omega_x$$

$$\Omega_x:=\{(x,y)\,|x\in\mathbb{R},y\in(0,\infty)\}\,.$$

Conclusion/Discussion

1. We analysed two models of stem cell maturation.
2. We considered two approximations of the chain of maturation stages.
3. We have focused on the existence of equilibrium points and their local stability properties using reproduction numbers.

compartment	Stability of positive eq.	
2	GAS (always)	The regulation mechanisms are efficient to achieve homeostasis.
3	Instability is possible	The intermediate stage of differentiation is responsible for the emergence of an instability region.

Future works

1. Stability analysis for DDE describing stem cell maturation.
2. Modeling breast cancer developing

One more thing–Modeling the maturity of cell

Maturity as a continuous process

At time t

Maturity level of a progenitor cell: $x \in [x_1, x_2]$
Age of a progenitor cell: s

Maturity level of progenitor cell at age $s : x(s)$

X_1 x_2

How do the progenitor cells mature?

Maturity velocity	depends **only** on the state $x'(s) = g(x(s)),$	Depends on the environment $x'(s) = g(x(s), v(t-a+s))$
		g: positive bounded function
The time required to mature	The solution of $\int_0^a g(x(s))ds = x_2 - x_1$	The solution of $\int_0^a g(x(s), v(t-a+s))ds = x_2 - x_1$
		a: state-dependent
Math. model	Diff. eq. with a fixed delay	Diff. eq. with a state-dependent delay (Alarcon et al., (to appear))

for your interest

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Research topics:

Nonlinear dynamical analysis,
Differential / difference equation systems
and its Applications.

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